REMARKS

Claims Considered

As stated in the Response filed July 9, 2008, applicant has elected the species of Example 5, and indicated that the claims covering this species are claims 1, 2, 5, 7, 8, and 10. Accordingly, claims 3, 4, 6, and 9 now stand withdrawn, and are indicated as such in the foregoing listing of claims. In addition, claim 5 is cancelled. The Office Action of April 15, 2008 considered only claims 1 and 8. In the July 9, 2008 response, it was respectfully submitted that claims 2, 7, and 10 also should be considered. It was pointed out that with regard to claim 2, the elected species of Example 5 is a diFab' conjugated molecule, i.e., one that contains two functionally active antibody fragments (Fab'). Claim 2 recites that Z^1, Z^2 and Z^3 each can be, *inter alia*, a functionally active antibody fragment. Accordingly, claim 2 covers the elected species, and should be considered. It was further pointed out that claim 7 recites the compound of claim 1 where n=0, and that, as stated in the Response of February 7, 2008, the compound of Example 5 is one in which n=0, such that claim 7 should be considered at this time. It was further pointed out that claim 10 is a pharmaceutical composition comprising the compound of claim 1, and therefore also should be considered at this time.

In the Office Action of October 16, 2008, the Examiner considered only claims 1 and 8, without considering claims 2, 7, and 10, and without commenting upon the explanation of why these claims are properly subject to examination on the merits at this time, as set forth above. It is respectfully requested that the present examination include claims 2, 7, and 10, or in the alternative that an explanation be given as to why those claims are not being considered at this time.

Written Description

Claims 1 and 8 stand rejected under 35 U.S.C 112 as lacking written description in the specification in relation to the claim term "residue," such as in the context of "residue of a polyethylene glycol (PEG) molecule." The language "residue" finds support in the specification at page 3, lines 19-20 and in claim 5 as originally filed. With regard to the Examiner's assertion that "Applicant has not provided a description as to how the base molecule may be changed while remaining a residue," the Examiner's attention is respectfully directed to page 3, lines 12-14 of the specification, where the term "residue" is

defined as "that portion of a polymer or of a biologically active moiety which remains after it has undergone a substitution reaction as such terminology is familiar to the person skilled in the art."

The Examiner's rejection of this term as lacking in written description is respectfully traversed. The Examiner's attention is directed to U.S. 6,251,382, cited on page 1, line 25 of the present specification. At column 4, lines 19-22, the '382 patent recites the following definition of "residue:" "For purposes of the present invention, the term 'residue' shall be understood to mean that portion of a biologically active compound or polymer which remains after it has undergone a substitution reaction as described herein." That definition is substantially identical to the definition of the same term as stated in the present specification. Further, the term "residue" appears in claims 1, 4-8, 12 and 13 of the '382 patent. As the term "residue' is being used in the identical sense in which it was used in the '382 patent, it is apparent that in issuing the '382 patent the USPTO made a determination that the use of the term "residue" in the context of such chemical compounds and biological substances is understood by those of skill in the art and is thus allowable.

Technical dictionaries confirm this understanding of the term "Residue" as used in the chemical and biological arts. For example, "Combinatorial Chemistry Review" at http://www.combichemistry.com/glossary_r.html defines "Residue" as

> "a) Portion of a chemical structure which can be identified as being derived from a particular building block; ..."

This is explained in greater detail at http://en.wikipedia.org/wiki/Residue_(chemistry) which states,

> "In biochemistry and molecular biology, a residue refers to a specific monomer within the polymeric chain of a polysaccharide, protein or nucleic acid. For example, one might say, *"The histidine residue is considered to be basic due to its imidazole ring."* Note that a residue is different from a moiety, which, in the above example would be constituted by the imidazole ring or "the imidazole moiety".
>
> "Note the origin of this usage: during the process by which monomeric building blocks (e.g. amino acids) are strung together into a polymeric chain (e.g. a protein), some material (typically adding up to one molecule of water) is discarded from each building block, and only a "residue" of the building block ends up in the finished product.
>
> "For example, a residue is an individual amino acid in a peptide chain."

Consistent with these defintions is the defintion of "Residue" at http://www.biology_online.org/dictionary/Residue, which states

> "(Science:biochemistry) A single unit within a polymer, such as an amino acid within a polypeptide or protein. The term reflects the fact that sugars, nucleotides, and amino acids usually lose a few atoms (usually hydrogen and oxygen) when they are polymerised into a larger molecule."

This same understanding is stated in the definition of "Residue" in the glossary of the standard text Lehringer Principles of Biochemistry, D.L. Nelson and M.M. Cox, Third Ed., Worth Publishers, copyright 2000:

> "A single unit within a polymer; for example, an amino acid within a polypeptide chain. The term reflects the fact that sugars, necleotides, and amino acids lose a few atoms (generally the elements of water) when incorporated in their respective polymers."

Copies of each of these on-line dictionary definitions and the textbook definition are submitted herewith.

The foregoing defintions are all consistent with the definition used in the present specification. "That portion of a polymer or of a biologically active moiety which remains after it has undergone a substitution reaction as such terminology is familiar to the person skilled in the art" means the portion of the polymer or biologically active moiety that remains attached to the particular structural formula after the substitution reaction which removes the elements of the corresponding water molecule, as is known to those skilled in the art, as evidenced by the foregoing definitions. To those skilled in the arts of chemistry and biochemistry, the term "residue of a polyethylene glycol (PEG) molecule" as used in the present claims would be understood to mean a portion of a polyethylene glycol (PEG) molecule that can be identified as being derived from a polyethylene glycol building block, or one or more ethylene glycol monomers, less the hydrogen or oxygen atoms that are lost during polymerization.

In the hypothetical example postulated by the examiner, namely, a PEG molecule having the structure maleimide-PEG-maleimide undergoing a substitution reaction to lose a terminal maleimide, the free maleimide would not be understood by those skilled in the art to be a PEG residue, because it cannot be identified as having been derived from a PEG molecule, nor is it a monomer of PEG, nor is it a portion of a PEG molecule that has lost the elements of water during polymerization.

Similarly, one skilled in the art would understand the claim term "residue of a polyclonal, monoclonal, multi-valent, multi-specific, humanized or chimeric antibody, a single chain antibody, a Fab fragment, a Fab' or $F(ab')_2$ fragment, or an epitope-binding fragment thereof" to be a portion of such an antibody or fragment that can be recognized as having been derived from such antibody or fragment, or the portion of such antibody or fragment that is bound to the structure of formula (I) after loss of the elements of water during the substitution reaction. And the term "maleimide residue" would be understood by one skilled in the art to be that portion of maleimide that remains when it binds to the structure of formula (I) after loss of elements of water during the substitution reaction, or which is otherwise recognizable as having been derived from maleimide.

The specification and claims are to be interpreted not in a vacuum but as they would be understood by those of skill in the art. In this case, the term "residue" is sufficiently well understood by those skilled in the chemical and biochemical arts that the present specification and claims satisfy the written description requirement under 35 USC 112.

35 USC §102

The rejection of the claims as anticipated by the Norman et al. reference is respectfully traversed. As the Examiner notes, in the Norman et al. reference the moieties P^1 and Z^1 are defined as 1-pentyl-1*H*-pyrrole-2,5-dione, and P^2 is defined as $OC(CH_3)_3$. Neither of these compounds is a "residue of a polyethylene glycol (PEG) molecule," as P^1 and P^2 are defined in claim 1, nor is 1-pentyl-1*H*-pyrrole-2,5-dione a "polyclonal, monoclonal, multi-valent, multi-specific, humanized or chimeric antibody, a single chain antibody, a Fab fragment, a Fab' or $F(ab')_2$ fragment, or an epitope-binding fragment thereof" as Z^1 is defined in claim 1. As explained above, neither of these entities are recognizable as having been derived from a PEG molecule or an antibody or antibody fragment, nor are they monomers thereof, nor are they a PEG molecule or antibody or fragment that has lost the elements of water when undergoing a substitution reaction to bind to the structure of formula (I). The Examiner's unsupported statement that "Thus, 1-pentyl-1*H*-pyrrole-2,5-dione and $OC(CH_3)_3$ could reasonably be considered residues of polyethylene glycol (PEG) molecules" (Office action page 4) is respectfully traversed, because it has been amply demonstrated that one skilled in the biochemical arts would not reasonably consider PEG residues to encompass such structures.

With regard to the B^2 structure, the Examiner's statement that "with only the recitation of the functional group and without further structural information, the broadest

reasonable interpretation of –CONH- would be one in which the functional group was oriented in either the fashion wherein the carbon atom is bonded to Y^2 and the nitrogen atom is bonded to V^2, or the reverse" (Office Action page 4) is respectfully traversed. Such a reading improperly views the claim element –CONH- in isolation. Instead, the claim element must be read in the context of both the entire claim of which it is a part, and the entire application.

Looking first to the claim, -NHCO- and –CONH- are not the same thing in the context of the presently claimed structures. In claim 1, where B^2 is defined as representing only –CONH- or –CO-, when B^2 is –CONH- the carbon atom will be bonded to V^2 and the nitrogen atom will be bonded Y^2. If B^2 were –NHCO- (a species not recited in the claim), the nitrogen atom would be bonded to V^2 and the carbon atom would be bonded to Y^2. By comparison, A^1 and A^2 are defined in claim 1 with -CONH- and -NHCO- both listed as alternative species, confirming that these are not the same in the context of the claimed structure.

Looking next to the specification, at page 5 lines 23-24, it is stated "Suitably, A^1 represents –CONH- or –NHCO. In one embodiment, A1 represents –CONH-. In another embodiment, A^1 represents –NHCO-." The same statements are made at lines 25-26 with respect to A^2. It is difficult to conceive of language that could more clearly state that for the purposes of this application –CONH- and -NHCO- are different structures. At page 5, line 28, the specification states, "In one embodiment, B^1 represents –CONH-." At line 31 that same statement is made for B^2. Nowhere is it said that B^1 or B^2 can be -NHCO-. Referring to the specification at page 11, line 7, there begins a description of a process for preparing a structure in which A^1 and A^2 are both –CONH-, while at page 13, line 6 there begins a description of a process for preparing a structure wherein A^1 and A^2 are both –NHCO-. As different processes for preparation of the different structures are both required and fully disclosed, it is abundantly clear that -CONH- and -NHCO- are not the same for the purposes of this patent application. At page 12 there is a description of a process for preparing a structure wherein B^1 and B^2 are both –CONH-. There is no description of a process for preparing a structure wherein B^1 and B^2 are -NHCO-. A structure wherein B^1 or B^2 is –NHCO- is neither disclosed nor claimed in the present application.

In the Office Action, the Examiner states that in the Norman et al. reference the B^2 moiety is -NHCO-. In claim 1, the B^2 moiety is –CONH-, which as demonstrated above cannot be construed to encompass –NHCO- when read in the context of the claim in its

entirety and the specification. Accordingly B^2 of the Norman reference is not the same as B^2 of the claim.

For the foregoing reasons, the Norman et al. reference does not anticipate claim 1, and withdrawal of this ground of rejection is respectfully requested.

CONCLUSION

Applicants respectfully submit that the present application is in condition for allowance. Favorable consideration and a notice of allowance of claims 1, 2, 7, 8, and 10 are respectfully requested.

Respectfully submitted,

Date: December 16, 2008

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Radiofrequency Encoding

Strategy for identifying library members by physically associating them with a set of electronic devices which emit characteristic radiofrequency signals upon stimulation with a radiofrequency energy source. These signals can be used to track the reaction history of each sample in a synthesis.

Ratio Coding
Encoding strategy in which the relative quantities of tags convey information about compound identity. In comparison to binary coding, more information may be obtained from a given tag set, but tag interpretation is more complex.

Receptor
A molecule within a cell or on a cell surface to which a substance (such as a hormone or a drug) selectively binds, causing a change in the activity of the cell.

Reagent Efficiency
The ratio of the number of library members prepared compared to the number which would have been prepared in a fully combinatorial library using the same building blocks. Lower reagent efficiency may be desirable in order to reduce the number of compounds to be synthesized or tested, for example by maximizing the number of members expected to have high activity in a library prepared by parallel synthesis.

Reagent Partitioning
Phenomenon whereby the concentration of a compound within, for instance, a particle of solid support is higher or lower than of the bulk solution due to the physicochemical properties of the solid support.

Recursive Partitioning
Process for identifying complex structure-activity relationships in large sets by dividing compounds into a hierarchy of smaller and more homogeneous sub-groups on the basis of the statistically most significant descriptors.

Residue
a) Portion of a chemical structure which can be identified as being derived from a particular building block;
b) portion of a building block which is incorporated into the final product but is not part of the scaffold.

Resin
Insoluble polymeric material which allows ready separation from liquid phase materials by filtration; can be used to carry library members (i.e. solid support) or reagents, or to trap excess reagents or reaction by-products.

Re-synthesis
Preparation of individual members or pools of a combinatorial library, normally to follow up on some property of interest identified in initial screening, and often in larger scale and/or greater purity than the original preparation.

Robotic System
Automated device where materials are transferred by the physical movement of a delivery device relative to the ultimate receptacle, or vice versa.

Rules of Five: Lipinski's rules
Set of criteria for predicting the oral bioavailability of a compound on the basis of simple molecular features (molecular weight, c Log P, numbers of hydrogen-bond donors and acceptors). Often used to profile a library or virtual library with respect to the proportion of drug-like members which it contains.

Residue (chemistry)

From Wikipedia, the free encyclopedia

In chemistry, **residue** refers to the material remaining after a distillation or an evaporation, or to a portion of a larger molecule, such as a methyl group.

In biochemistry and molecular biology, a residue refers to a specific monomer within the polymeric chain of a polysaccharide, protein or nucleic acid. For example, one might say, *"The histidine residue is considered to be basic due to its imidazole ring."* Note that a residue is different from a moiety, which, in the above example would be constituted by the imidazole ring or "the imidazole moiety".

Note the origin of this usage: during the process by which monomeric building blocks (e.g. amino acids) are strung together into a polymeric chain (e.g. a protein), some material (typically adding up to one molecule of water) is discarded from each building block, and only a "residue" of the building block ends up in the finished product.

For example, a residue is an individual amino acid in a peptide chain.

Retrieved from "http://en.wikipedia.org/wiki/Residue_(chemistry)"
Category: Chemistry stubs

Residue

residue

(Science: biochemistry) A single unit within a polymer, such as an amino acid within a polypeptide or protein.

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Lehninger Principles of Biochemistry

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replication fork: The Y-shaped structure generally found at the point where DNA is being synthesized.

replicative form: Any of the full-length structural forms of a viral chromosome that serve as distinct replication intermediates.

replisome: The multiprotein complex that promotes DNA synthesis at the replication fork.

repressible enzyme: In bacteria, an enzyme whose synthesis is inhibited when its reaction product is readily available to the cell.

repression: A decrease in the expression of a gene in response to a change in the activity of a regulatory protein.

repressor: The protein that binds to the regulatory sequence or operator for a gene, blocking its transcription.

residue: A single unit within a polymer; for example, an amino acid within a polypeptide chain. The term reflects the fact that sugars, nucleotides, and amino acids lose a few atoms (generally the elements of water) when incorporated in their respective polymers.

respiration: Any metabolic process that leads to the uptake of oxygen and the release of CO_2.

respiration-linked phosphorylation: ATP formation from ADP and P_i, driven by electron flow through a series of membrane-bound carriers, with a proton gradient as the direct source of energy driving rotational catalysis by ATP synthase.

respiratory chain: The electron transfer chain; a sequence of electron-carrying proteins that transfer electrons from substrates to molecular oxygen in aerobic cells.

restriction endonucleases: Site-specific endodeoxyribonucleases causing cleavage of both strands of DNA at points within or near the specific site recognized by the enzyme; important tools in genetic engineering.

restriction fragment: A segment of double-stranded DNA produced by the action of a restriction endonuclease on a larger DNA.

restriction fragment length polymorphisms (RFLPs): Variations, among individuals in a population, in the length of certain restriction fragments within which certain genomic sequences occur. These variations result from rare sequence changes that create or destroy restriction sites in the genome.

retrovirus: An RNA virus containing a reverse transcriptase.

reverse transcriptase: An RNA-directed DNA polymerase in retroviruses; capable of making DNA complementary to an RNA.

ribonuclease: A nuclease that catalyzes the hydrolysis of certain internucleotide linkages of RNA.

ribonucleic acid: *See* RNA.

ribonucleotide: A nucleotide containing D-ribose as its pentose component.

ribosomal RNA (rRNA): A class of RNA molecules serving as components of ribosomes.

ribosome: A supramolecular complex of rRNAs and proteins, approximately 18 to 22 nm in diameter; the site of protein synthesis.

ribozymes: Ribonucleic acid molecules with catalytic activities; RNA enzymes.

Rieske iron-sulfur protein: A type of iron-sulfur protein in which two of the ligands to the central iron ion are His side chains. These proteins act in many electron-transfer sequences, including oxidative phosphorylation and photophosphorylation.

RNA (ribonucleic acid): A polyribonucleotide of a specific sequence linked by successive 3′, 5′-phosphodiester bonds.

RNA polymerase: An enzyme that catalyzes the formation of RNA from ribonucleoside 5′-triphosphates, using a strand of DNA or RNA as a template.

RNA splicing: Removal of introns and joining of exons in a primary transcript.

rRNA: *See* ribosomal RNA.

S

***S*-adenosylmethionine (adoMet):** An enzymatic cofactor involved in methyl group transfers.

salvage pathway: Synthesis of a biomolecule, such as a nucleotide, from intermediates in the degradative pathway for the biomolecule; a recycling pathway, as distinct from a de novo pathway.

saponification: Alkaline hydrolysis of triacylglycerols to yield fatty acids as soaps.

sarcomere: A functional and structural unit of the muscle contractile system.

satellite DNA: Highly repeated, nontranslated segments of DNA in eukaryotic chromosomes; most often associated with the centromeric region. Its function is not clear.

saturated fatty acid: A fatty acid containing a fully saturated alkyl chain.

second law of thermodynamics: The law stating that in any chemical or physical process, the entropy of the universe tends to increase.

second messenger: An effector molecule synthesized within a cell in response to an external signal (first messenger) such as a hormone.

secondary metabolism: Pathways that lead to specialized products not found in every living cell.

secondary structure: The residue-by-residue conformation of the backbone of a polymer.

sedimentation coefficient: A physical constant specifying the rate of sedimentation of a particle in a centrifugal field under specified conditions.

selectins: A large family of membrane proteins, lectins that bind oligosaccharides on other cells tightly and specifically, and serve to carry signals across the plasma membrane.

SELEX: A method for rapid experimental identification of nucleic acid sequences (usually RNA) that have particular catalytic or ligand-binding properties.

serpentine receptors: A large family of membrane receptor proteins with seven transmembrane helical segments. These receptors often associate with G proteins to transduce an extracellular signal into a change in cellular metabolism.

Shine-Dalgarno sequence: A sequence in an mRNA required for binding prokaryotic ribosomes.

SH2 domain: A protein domain that binds tightly to a phosphotyrosine residue in certain proteins such as the receptor tyrosine kinases initiating the formation of a multiprotein complex that acts in a signaling pathway.

shuttle vector: A recombinant DNA vector that can be replicated in two or more different host species. *See also* vector.

sickle-cell anemia: A human disease characterized by defective hemoglobin molecules; caused by a homozygous allele coding for the β chain of hemoglobin.

sickle-cell trait: A human condition recognized by the sickling of erythrocytes when exposed to low oxygen tension; occurs in individuals heterozygous for the allele responsible for sickle cell anemia.

signal sequence: An amino acid sequence, often at the amino terminus, that signals the cellular fate or destination of a newly synthesized protein.

signal transduction: The process by which an extracellular signal (chemical, mechanical, or electrical) is amplified and converted to a cellular response.

silent mutation: A mutation in a gene that causes no detectable change in the biological characteristics of the gene product.

simple diffusion: The movement of solute molecules across a membrane to a region of lower concentration, unassisted by a protein transporter.

simple protein: A protein yielding only amino acids on hydrolysis.

site-directed mutagenesis: A set of methods used to create specific alterations in the sequence of a gene.

site-specific recombination: A type of genetic recombination that occurs only at specific sequences.

size-exclusion chromatography: A process for the separation of a mixture of molecules on the basis of size, based on the capacity of porous polymers to exclude solutes above a certain size. Also called gel filtration.

small nuclear RNA (snRNA): Any of several small RNA molecules in the nucleus; most have a role in the splicing reactions that remove introns from mRNA, tRNA, and rRNA molecules.

somatic cells: All body cells except the germline cells.

SOS response: In bacteria, a coordinated induction of a variety of genes as a response to high levels of DNA damage.

Southern blot: A DNA hybridization process in which one or more specific DNA fragments are detected in a larger population by means of